REMARKS

Claims 8, 9, 15, and 16 currently appear in this application. The Office Action of April 10, 2001, has been carefully studied. These claims define novel and unobvious subject matter under Sections 102 and 103 of 35 U.S.C., and therefore should be allowed. Applicants respectfully request favorable reconsideration, entry of the present amendment, and formal allowance of the claims.

Election/Restriction

The nonelected claims, claims 12-14 and 19-21, have been cancelled by the present amendment.

Art Rejections

The subject matter of the various claims was commonly owned at the time that the inventions covered in the claims were made.

Claims 8-11 and 15-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over "The Pharmacological Basis of Therapeutics" in view of Hukkanen et al. and Moore et al. The Examiner alleges that Moore et al. teach that L-N-6-(1-iminomethyl)lysine is a potent and selective iNOS inhibitor. Hukkanen et al. are said to teach that iNOS inhibitors completely inhibit the activity of cytokines such as IL-6, which are known to increase bone

resorption and decrease bone mass as taught by Therapeutics. Therapeutics is also said to teach that medications that inhibit the activity of IL-6 are useful in conserving bone mass.

This rejection is respectfully traversed. The Examiner noted that the feature on which applicant relies, namely, a bone mass-maintenance drugs, or a drug for maintaining bone mass, are not recited in the rejected claims. Accordingly, claims 8 and 15 have been amended to recite this feature of the invention. This amendment incorporates the limitations of claims 10 and 17 into claims 8 and 15, respectively. Therefore, claims 10 and 17, along with claims 11 and 18, directed to bone resorption retardant, have been cancelled.

Therapeutics describes a treatment of osteoporosis by decreasing the rate of bone resorption. However, it is also noted at page 1540, right column, second paragraph, lines 7-9, that antiresorptive therapy cannot lead to substantial gain in bone mass. Therefore, even if a substance having a bone resorptive activity is known, one of ordinary skill in the art would not reach a method for treating a bone resorption-associated disease by

maintaining bone mass given the disclosure in Therapeutics taken with Hukkanen et al. and Moore et al.

Hukkanen et al. describes the role of NO in a bone destruction model associated with inflammatory bone diseases such as rheumatoid arthritis (see abstract and page 5452, right column, final paragraph) rather than in metabolic bone disease models. This is apparent from the fact that cells used therein were stimulated with proinflammatory cytokines such as IL-1β and TNF-α (see page 5446, "Cell cultures" in Materials and Methods). That is, the treatment technique for the diseases treated by Hukkanen et al. is different from that of the present invention. Moreover, with respect to the effect of NO, there is no relation between knowledge generally available to one or ordinary skill in the art in the fields of rheumatoid arthritis and osteoporosis; the effects exhibited by NO are diverse. Hukkanen et al. describe that prototypic NOS inhibitors have a significant effect on suppression of arthritis and local bone destruction in experimental rat models. On the other hand, Hukkanen et al. note that NO may have a preferential role as an inhibitor of osteoclast activity *in vitro* and *in vivo* (see page 5446, left column, lines 20-27). NO function in an

osteoporosis model is further supported by the following documents, copies of which are submitted herewith:

Kasten et al., *Proc. Natl. Acad. Sci. USA* **91**m 3569-3573, 1994

Evans et al, *J. Bone Miner. Res.* **11** 300-305, 1996

Turner et al., *Am. J. Physiol.* **270**, E634-E639, 1996;

Fox et al., *Am. J. Physiol.* **270**, E955-E960, 1996

Wimalawansa et al., *Bone* **18(4)** 301-304, 1996

Riancho et al., *Mol. Cell Endocrinol* **107** 87-92, 1995

The above articles have reported that supplementation of NO, rather than inhibition of NO production, is effective in treating osteoporosis. Accordingly, it is apparent that Hukkanen et al. have nothing to do with the present invention. Even if the teaching that NOS inhibitors completely inhibit activity of cytokines such as IL-6 is applied to the case of bone destruction model such as rheumatoid arthritis, it cannot be directly applied in the case of osteoporosis.

Moore et al. merely disclose that L-N-6-(1-iminoethyl)lysine is a potent and selective inhibitor of iNOS.

As the Federal Circuit stated in *In re Lee*, 61

USPQ2d 1430 (January 18, 2002, Fed. Cir.), "As applied to the determination of patentability *vel non*, when the issue is obviousness, 'it is fundamental that rejections under 35 U.S.C. 103 must be based on evidence comprehended by the language of that section.' *In re Grasselli*, 53 USPQ2d 1769, 1774 (Fed. Cir. 2000)... When patentability turns on the question of obviousness, the search for an analysis of the prior art includes evidence relevant to the finding of whether there is a teaching, motivation, or suggestion to select and combine the references relied on as evidence of obviousness *See, e.g., McGinley v. Franklin Sports, Inc*, 60 USPQ2d 1001, 1008 (Fed. Cir. 2001) "'the central question is whether there is a reason to combine [the] references,' a question of fact drawing on the *Graham* factors."

'The factual inquiry whether to combine references must be thorough and searching.' *Id.* This precedent has been reinforced in myriad decisions, and cannot be dispensed with, *See, e.g., Brown & Williamson Tobacco Corp. v. Philip Morris, Inc.*, 56 USPQ2d 1456, 1459 (Fed. Cir. 2000). ("'a showing of a suggestion, teaching, or motivation to combine the prior art references is an "essential component of an obviousness holding"') (quoting *C. R. Bard, Inc. v. M3 Systems, Inc.* 48 USPQ2d (Fed. Cir.

1998)) The Court went on to quote *In re Dembiczak*, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999), "Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references."

There is a requirement for specificity in combining references, *See, In re Kotzab*, 55 USPQ2d 13134, 1317 (Fed. Cir. 2002)("particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed."). Therefore, since Hukkanen et al. is irrelevant to the present invention, it is not proper to combine Hukkanen et al. with Moore et al. and Therapeutics.

In view of the above, it is respectfully submitted that one of ordinary skill in the art would not be motivated to use a NOS inhibitor in treating osteoporosis by combining Therapeutics and Moore et al., since Hukkanen et al. is irrelevant to the present invention. Since Hukkanen et al. is an improper citation, it is unreasonable to combine Therapeutics with Hukkanen et

al., as well as to combine Therapeutics with Hukkanen et al and Moore et al.

In view of the above, it is respectfully submitted that the claims are now in condition for allowance, and favorable action thereon is earnestly solicited.

Respectfully submitted,

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8. (Amended) A method for treating a bone resorption-associated disease comprising administering to a subject in need thereof an effective amount of a selective iNOS inhibitor **as a bone mass-maintenance drug to maintain bone mass**.

15. (Amended) A kit for treating a bone resportion-associated disease comprising an effective amount of a selective iNOS inhibitor **as a bone mass-maintenance drug to maintain bone mass** and instructions for treating a bone resorption-associated disease.